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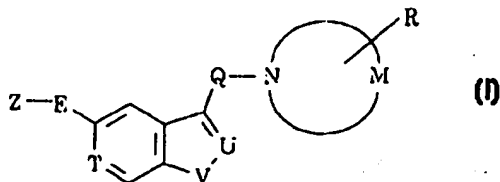
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(71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED (GB/GB); Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB).			
(72) Inventors; and (75) Inventors/Applicants (for US only): BOURRAIN, Sylvie (FR/GB); Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). MACLEOD, Angus, Murray (GB/GB); Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). SHOWELL, Graham, Andrew (GB/GB); Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). STREET, Leslie, Joseph (GB/GB); Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).		Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(74) Agent: THOMPSON, John; Merck & Co., Inc., European Patent Dept., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).			

(54) Title: AZETIDINE, PYRROLIDINE AND PIPERIDINE DERIVATIVES AS 5-HT_{1D} RECEPTOR AGONISTS

(57) Abstract

A class of substituted azetidine, pyrrolidine and piperidine derivatives of formula (I) are selective agonists of 5-HT₁-like receptors, being potent agonists of the human 5-HT_{1D} receptor subtype whilst possessing at least a 10-fold selective affinity for the 5-HT_{1D} receptor subtype relative to the 5-HT_{1A} subtype; they are therefore useful in the treatment and/or prevention of clinical conditions, in particular migraine and associated disorders, for which a subtype-selective agonist of 5-HT_{1D} receptors is indicated, whilst eliciting fewer side-effects, notably adverse cardiovascular events, than those associated with non-subtype-selective 5-HT_{1D} receptor agonists, wherein Z represents an optionally substituted six-membered heteroaromatic ring selected from pyridine, pyrazine, pyrimidine and pyridazine; E represents a chemical bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms; Q represents a straight or branched alkylene chain containing from 1 to 4 carbon atoms, optionally substituted in any position by one or more substituents selected from fluoro and hydroxy; T represents nitrogen or CH; U represents N or CR². V = O, S or NR³. M & R are as defined in the application.



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AZETIDINE, PYRROLIDINE AND PIPERIDINE DERIVATIVES AS 5-HT_{1D} RECEPTOR AGONISTS

The present invention relates to a class of substituted azetidine,
5 pyrrolidine and piperidine derivatives which act on 5-hydroxytryptamine
(5-HT) receptors, being selective agonists of so-called "5-HT_{1-like}"
receptors. They are therefore useful in the treatment of clinical conditions
for which a selective agonist of these receptors is indicated.

It has been known for some time that 5-HT_{1-like} receptor agonists
10 which exhibit selective vasoconstrictor activity are of use in the treatment
of migraine (see, for example, A. Doenicke *et al.*, *The Lancet*, 1988, Vol. 1,
1309-11; and W. Feniuk and P.P.A. Humphrey, *Drug Development
Research*, 1992, 26, 235-240).

The human 5-HT_{1-like} or 5-HT_{1D} receptor has recently been shown
15 by molecular cloning techniques to exist in two distinct subtypes. These
subtypes have been termed 5-HT_{1D α} (or 5-HT_{1D.1}) and 5-HT_{1D β} (or
5-HT_{1D.2}), and their amino acid sequences are disclosed and claimed in
WO-A-91/17174.

The 5-HT_{1D α} receptor subtype in humans is believed to reside on
20 sensory terminals in the dura mater. Stimulation of the 5-HT_{1D α} subtype
inhibits the release of inflammatory neuropeptides which are thought to
contribute to the headache pain of migraine. The human 5-HT_{1D β} receptor
subtype, meanwhile, is located predominantly on the blood vessels and in
the brain, and hence may play a part in mediating constriction of cerebral
25 and coronary arteries, as well as CNS effects.

Administration of the prototypical 5-HT_{1D} agonist sumatriptan
(GR43175) to humans is known to give rise at therapeutic doses to certain
adverse cardiovascular events (see, for example, F. Willett *et al.*, *Br. Med.
J.*, 1992, 304, 1415; J.P. Ottervanger *et al.*, *The Lancet*, 1993, 341, 861-2;
30 and D.N. Bateman, *The Lancet*, 1993, 341, 221-4). Since sumatriptan
barely discriminates between the human 5-HT_{1D α} and 5-HT_{1D β} receptor

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subtypes (cf. WO-A-91/17174, Table 1), and since it is the blood vessels with which the 5-HT_{1D β} subtype is most closely associated, it is believed that the cardiovascular side-effects observed with sumatriptan can be attributed to stimulation of the 5-HT_{1D β} receptor subtype. It is accordingly
5 considered (cf. G.W. Rebeck *et al.*, *Proc. Natl. Acad. Sci. USA*, 1994, **91**, 3666-9) that compounds which can interact selectively with the 5-HT_{1D α} receptor subtype, whilst having a less pronounced action at the 5-HT_{1D β} subtype, might be free from, or at any rate less prone to, the undesirable cardiovascular and other side-effects associated with non-subtype-selective
10 5-HT_{1D} receptor agonists, whilst at the same time maintaining a beneficial level of anti-migraine activity.

The compounds of the present invention, being selective 5-HT₁-like receptor agonists, are accordingly of benefit in the treatment of migraine and associated conditions, e.g. cluster headache, chronic paroxysmal
15 hemicrania, headache associated with vascular disorders, tension headache and paediatric migraine. In particular, the compounds according to this invention are potent agonists of the human 5-HT_{1D α} receptor subtype. Moreover, the compounds in accordance with this invention have been found to possess at least a 10-fold selective affinity for
20 the 5-HT_{1D α} receptor subtype relative to the 5-HT_{1D β} subtype, and they can therefore be expected to manifest fewer side-effects than those associated with non-subtype-selective 5-HT_{1D} receptor agonists.

WO-A-94/08993 and WO-A-95/28400 describe substituted pyridinyl-benzofuran derivatives, and analogues thereof. These compounds are
25 stated therein to be selective agonists at 5-HT₁-like receptors and thus useful in treating conditions associated with cephalic pain, including migraine. Neither of these publications, however, discloses or even suggests the substituted azetidine, pyrrolidine and piperazine derivatives provided by the present invention.

30 Moreover, nowhere in the prior art mentioned above is there any disclosure of a subtype-selective 5-HT_{1D} receptor agonist having a 5-HT_{1D α}

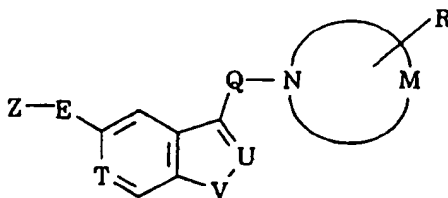
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receptor binding affinity (IC_{50}) below 50 nM and at least a 10-fold selective affinity for the 5-HT_{1D α} receptor subtype relative to the 5-HT_{1D β} subtype.

WO-A-95/32196, WO-A-96/04269 and WO-A-96/04274 describe various classes of heterocyclic compounds as alpha subtype-selective agonists of the human 5-HT_{1D} receptor. However, there is no disclosure or suggestion in any of these publications of the substituted six-membered heteroaromatic ring-containing compounds provided by the present invention.

The compounds according to the present invention are subtype-selective 5-HT_{1D} receptor agonists having a human 5-HT_{1D α} receptor binding affinity (IC_{50}) below 50 nM, typically below 10 nM and preferably below 1 nM; and at least a 10-fold selective affinity, typically at least a 50-fold selective affinity and preferably at least a 100-fold selective affinity, for the human 5-HT_{1D α} receptor subtype relative to the 5-HT_{1D β} subtype. Moreover, the compounds in accordance with this invention possess interesting properties in terms of their efficacy and/or bioavailability.

The present invention provides a compound of formula I, or a salt or prodrug thereof:



20

(I)

wherein

Z represents an optionally substituted six-membered heteroaromatic ring selected from pyridine, pyrazine, pyrimidine and pyridazine;

25

E represents a chemical bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

Q represents a straight or branched alkylene chain containing from 1 to 4 carbon atoms, optionally substituted in any position by one or more substituents selected from fluoro and hydroxy;

T represents nitrogen or CH;

5 U represents nitrogen or C-R²;

V represents oxygen, sulphur or N-R³;

R² and R³ independently represent hydrogen or C₁₋₆ alkyl;

M represents the residue of an azetidine, pyrrolidine or piperidine ring;

10 R represents a group of formula -W-R¹;

W represents a chemical bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms, optionally substituted in any position by a hydroxy group;

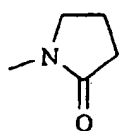
R¹ represents -OR^x, -SR^x, -SOR^x, -SO₂R^x or -NR^xR^y; and

15 R^x and R^y independently represent hydrogen, hydrocarbon or a heterocyclic group; or R^x and R^y together represent a C₂₋₆ alkylene group, which alkylene group may be optionally substituted by one or more substituents selected from C₁₋₆ alkyl, aryl and hydroxy, or fused with a phenyl ring.

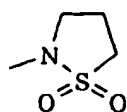
20 The six-membered heteroaromatic ring Z in the compounds of formula I above may be optionally substituted by one or more substituents, typically by one or two substituents. Examples of suitable substituents on the six-membered heteroaromatic ring Z include C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, halogen, halo(C₁₋₆)alkyl, cyano, cyano(C₁₋₆)alkyl, trifluoromethyl, and -(CH₂)_a-R⁴, in which a is zero, 1, 2 or 3 (preferably zero or 1) and R⁴ represents -OR^a, -OCOR^c, -OCO₂R^a, -SR^a, -SOR^a, -SO₂R^c, -CH=CHSO₂R^c, -SO₂NR^aR^b, -CH=CHSO₂NR^aR^b, -NR^aR^b, -NR^aCOR^c, -NR^aCO(CH₂)_bOR^d (in which b is 1 or 2, preferably 1), 25 -NR^aCO₂R^d, -NR^aSO₂R^c, -NR^dCONR^aR^b, -NR^dSO₂NR^aR^b, -COR^c, 30

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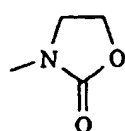
$-\text{CH}=\text{CHCOR}^c$, $-\text{CO}_2\text{R}^a$, $-\text{CONR}^a\text{R}^b$, $-\text{CH}=\text{CHCONR}^a\text{R}^b$, or $-\text{CONR}^d\text{NR}^a\text{R}^b$,
or R^4 represents a group of formula (a), (b), (c), (d) or (e):



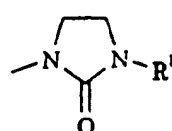
(a)



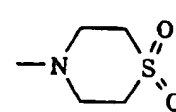
(b)



(c)



(d)



(e)

5

wherein R^a and R^d independently represent hydrogen, C_{1-6} alkyl, trifluoromethyl, phenyl, fluorophenyl or tetrahydropyranyl; R^b represents hydrogen, C_{1-6} alkyl, trifluoromethyl, phenyl or fluorophenyl; and R^c represents hydrogen, C_{1-6} alkyl, trifluoromethyl, phenyl, fluorophenyl, tetrahydropyranyl, azetidiny, pyrrolidinyl, piperidinyl or morpholinyl.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups containing up to 18 carbon atoms, suitably up

to 15 carbon atoms, and conveniently up to 12 carbon atoms. Suitable hydrocarbon groups include C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, indanyl, aryl and aryl(C₁₋₆)alkyl.

The expression "a heterocyclic group" as used herein includes cyclic groups containing up to 18 carbon atoms and at least one heteroatom preferably selected from oxygen, nitrogen and sulphur. The heterocyclic group suitably contains up to 15 carbon atoms and conveniently up to 12 carbon atoms, and is preferably linked through carbon. Examples of suitable heterocyclic groups include C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, heteroaryl and heteroaryl(C₁₋₆)alkyl groups.

Suitable alkyl groups include straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl, butyl and pentyl groups. Particular alkyl groups are methyl, ethyl, *n*-propyl, isopropyl, isobutyl, *tert*-butyl and 2,2-dimethylpropyl.

Suitable alkenyl groups include straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl, allyl and dimethylallyl groups.

Suitable alkynyl groups include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

Suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl and cyclohexyl.

Typical examples of C₃₋₇ cycloalkyl(C₁₋₆)alkyl groups include cyclopropylmethyl, cyclohexylmethyl and cyclohexylethyl.

Particular indanyl groups include indan-1-yl and indan-2-yl.

Particular aryl groups include phenyl and naphthyl.

Particular aryl(C₁₋₆)alkyl groups include benzyl, phenylethyl, phenylpropyl and naphthylmethyl.

Suitable heterocycloalkyl groups include azetidiny, pyrrolidiny, piperidiny, piperaziny and morpholiny groups.

Suitable heteroaryl groups include pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl groups.

The expression "heteroaryl(C₁₋₆)alkyl" as used herein includes furylmethyl, furylethyl, thienylmethyl, thienylethyl, oxazolylmethyl, oxazolylethyl, thiazolylmethyl, thiazolylethyl, imidazolylmethyl, imidazolylethyl, oxadiazolylmethyl, oxadiazolylethyl, thiadiazolylmethyl, thiadiazolylethyl, triazolylmethyl, triazolylethyl, tetrazolylmethyl, tetrazolylethyl, pyridinylmethyl, pyridinylethyl, pyrimidinylmethyl, pyrazinylmethyl, quinolinylmethyl and isoquinolinylmethyl.

The hydrocarbon and heterocyclic groups may in turn be optionally substituted by one or more groups selected from C₁₋₆ alkyl, adamantyl, phenyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ aminoalkyl, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, aryloxy, keto, C₁₋₃ alkylenedioxy, nitro, cyano, carboxy, C₂₋₆ alkoxycarbonyl, C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl, C₂₋₆ alkylcarbonyloxy, arylcarbonyloxy, aminocarbonyloxy, C₂₋₆ alkylcarbonyl, arylcarbonyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulphinyl, C₁₋₆ alkylsulphonyl, arylsulphonyl, -NR^vR^w, -NR^vCOR^w, -NR^vCO₂R^w, -NR^vSO₂R^w, -CH₂NR^vSO₂R^w, -NHCONR^vR^w, -CONR^vR^w, -SO₂NR^vR^w and -CH₂SO₂NR^vR^w, in which R^v and R^w independently represent hydrogen, C₁₋₆ alkyl, aryl or aryl(C₁₋₆)alkyl, or R^v and R^w together represent a C₂₋₆ alkylene group.

When R^x and R^y, or R^v and R^w, together represent a C₂₋₆ alkylene group, this group may be an ethylene, propylene, butylene, pentamethylene or hexamethylene group, preferably butylene or pentamethylene.

When R^x and R^y together represent a C₂₋₆ alkylene group, this group may be unsubstituted or substituted by one or more substituents selected from C₁₋₆ alkyl, aryl and hydroxy. Typical substituents include methyl, phenyl and hydroxy.

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Furthermore, when R^x and R^y together represent a C_{2-6} alkylene group, this group may optionally be fused with a phenyl ring. In this context, a typical group of formula $-NR^xR^y$ as defined for the substituent R^1 is 1,2,3,4-tetrahydroisoquinolinyl.

5 The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine.

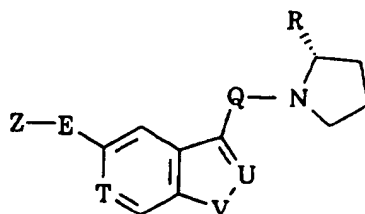
 The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily
10 convertible *in vivo* into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in *Design of Prodrugs*, ed. H. Bundgaard, Elsevier, 1985.

 Certain compounds according to the present invention may be
15 capable of existing as tautomeric forms. For example, a hydroxypyridine derivative in accordance with the invention may exist in admixture with its tautomeric pyridone isomer. It is to be understood that all possible tautomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

20 Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion
25 are encompassed within the scope of the present invention.

 In particular, where M represents the residue of a pyrrolidine ring, and the substituent R is attached to the 2-position thereof, then the absolute stereochemical configuration of the carbon atom at the point of attachment of the moiety R is preferably as depicted in structure IA as
30 follows:

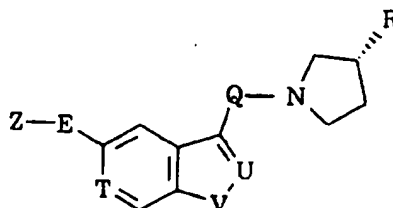
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(IA)

wherein Z, E, Q, T, U, V and R are as defined above.

Moreover, where M represents the residue of a pyrrolidine ring, and the substituent R is attached to the 3-position thereof, then the absolute stereochemical configuration of the carbon atom at the point of attachment of the moiety R is preferably as depicted in structure IB as follows:



(IB)

wherein Z, E, Q, T, U, V and R are as defined above.

The optionally substituted six-membered heteroaromatic ring Z in formula I is suitably a pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrazin-2-yl, pyrazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyridazin-3-yl or pyridazin-4-yl ring, especially pyridin-3-yl or pyrimidin-5-yl.

The six-membered heteroaromatic ring Z is unsubstituted or substituted by one or more substituents, typically by one or two substituents. Examples of optional substituents which may typically be attached to the moiety Z include methyl, methoxy, methoxycarbonyl, methoxymethyl, aminomethyl, dimethylaminomethyl, acetylaminomethyl, benzoylaminomethyl, *tert*-butoxycarbonylaminomethyl, methylsulphonylaminomethyl, phenylsulphonylaminomethyl, aminocarbonylmethyl, ethyl, aminoethyl, acetylaminomethyl, benzoylaminoethyl, methoxycarbonylaminoethyl,

ethoxycarbonylaminoethyl, *tert*-butoxycarbonylaminoethyl,
methysulphonylaminoethyl, aminocarbonylaminoethyl,
methylaminocarbonylaminoethyl, *tert*-butylaminocarbonylaminoethyl,
phenylaminocarbonylaminoethyl, pyrrolidinylcarbonylaminoethyl,
5 cyclopropyl, phenyl, naphthyl, benzyl, phenylethyl, phenylpropyl,
pyridinylmethyl, amino, methylamino, dimethylamino, aminocarbonyl,
methylaminocarbonyl, azetidiny carbonyl and pyrrolidinylcarbonyl.

Particular substituents which may be attached to the moiety Z
include methoxycarbonyl, methoxymethyl and methysulphonyl-
10 aminomethyl.

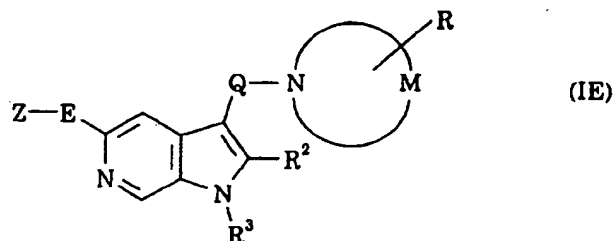
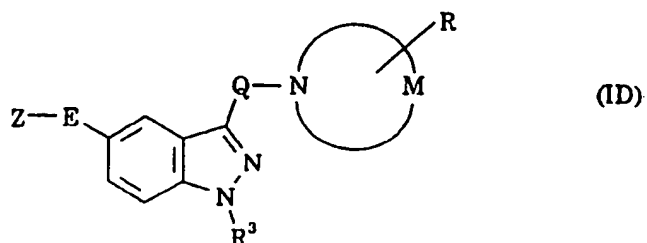
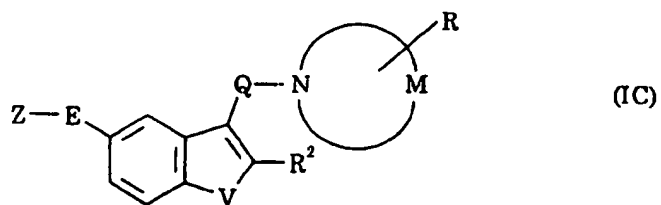
Where E, Q and W, which may be the same or different, represent
straight or branched alkylene chains, these may be, for example,
methylene, ethylene, 1-methylethylene, propylene, 2-methylpropylene or
butylene. In addition, Q and W may be substituted in any position by a
15 hydroxy group giving rise, for example, to a hydroxymethyl-methylene,
2-hydroxypropylene or 2-hydroxymethyl-propylene linkage. Moreover, Q
may be substituted in any position by one or more fluorine atoms giving
rise, for example, to a 2-fluoropropylene, 2,2-difluoropropylene or 2-
fluoromethyl-propylene linkage. Furthermore, E and W may each
20 independently represent a chemical bond. Where E represents a chemical
bond, the moiety Z is attached directly to the central fused bicyclic
heteroaromatic ring system containing the variables T, U and V.
Similarly, where W represents a chemical bond, the substituent R¹ is
attached directly to the azetidine, pyrrolidine or piperidine ring of which
25 M is the residue.

Suitably, E represents a chemical bond or a methylene linkage.

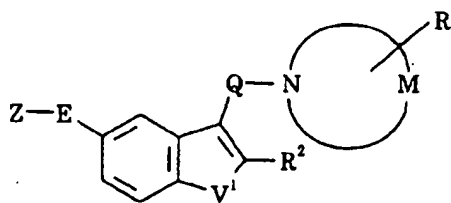
Suitably, Q represents an ethylene or propylene linkage.

The compound of formula I in accordance with the present invention
is suitably an indole, benzofuran or benzthiophene derivative of formula
30 IC, an indazole derivative of formula ID, or a pyrrolo[2,3-c]pyridine
derivative of formula IE:

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wherein Z, E, Q, V, M, R, R² and R³ are as defined above. Typically, the
 5 compounds according to the invention are indole or benzofuran derivatives
 of formula IF:



(IF)

wherein V¹ represents oxygen or N-R³, and Z, E, Q, M, R, R² and R³ are as
 defined above, in particular wherein R² and R³ are both hydrogen.

Suitably, W represents a chemical bond or a methylene or hydroxymethyl-methylene linkage, in particular a chemical bond or a methylene linkage.

- Suitably, R^x and R^y independently represent hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, indanyl, aryl, aryl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents selected typically from C₁₋₆ alkyl, halogen, hydroxy, C₁₋₆ alkoxy, aminocarbonyloxy, amino, C₂₋₆ alkylcarbonylamino, C₁₋₆ alkylsulphonylamino and C₁₋₆ alkylaminosulphonylmethyl. Particular values of R^x and R^y include hydrogen, methyl, hydroxyethyl, isobutyl, 2,2-dimethylpropyl, allyl, dimethylallyl, 1-cyclohexylethyl, 2-cyclohexylethyl, indanyl, hydroxy-indanyl, phenyl, benzyl, methyl-benzyl, fluorobenzyl, methoxy-benzyl, acetylamino-benzyl, 1-phenylethyl, 2-phenylethyl, 2-hydroxy-1-phenylethyl, 2-methoxy-1-phenylethyl, 2-aminocarbonyloxy-1-phenylethyl, 1-(fluorophenyl)ethyl, 1-(fluorophenyl)-2-hydroxyethyl, 1-(fluorophenyl)-2-methoxyethyl, 1-(acetylamino-phenyl)ethyl, 2-(acetylamino-phenyl)ethyl, 2-hydroxy-1-phenylprop-1-yl, 1-phenylprop-2-yl, 2-phenylprop-2-yl, 1-hydroxy-1-phenylprop-2-yl, 1-hydroxy-2-phenylprop-2-yl, 1-hydroxy-3-phenylprop-2-yl, furylmethyl, thienylmethyl and pyridylmethyl.

Specific values of R^x and R^y include methyl, benzyl and 1-phenylethyl.

- In addition, where R^x and R^y together represent an optionally substituted or phenyl ring-fused C₂₋₆ alkylene group, the substituent -NR^xR^y as defined for R¹ may suitably represent 3,3-dimethylpiperidinyl, 2-phenylpiperidinyl, 3-hydroxy-2-phenylpiperidinyl or 1,2,3,4-tetrahydroisoquinolin-2-yl.

- Suitable values for the substituent R¹ include hydroxy, benzyloxy, methoxy-benzyloxy, pyridylmethoxy, benzylthio, fluorobenzyl-thio, phenylsulphinyl, benzylsulphinyl, fluorobenzyl-sulphinyl, fluorobenzyl-sulphonyl, amino, methylamino, indanylamino, hydroxyindanyl-amino,

benzylamino, *N*-(methylbenzyl)-amino, *N*-(acetylamino-benzyl)-amino, *N*-(1-phenylethyl)-amino, *N*-(2-phenylethyl)-amino, *N*-(2-hydroxy-1-phenylethyl)-amino, *N*-(2-methoxy-1-phenylethyl)-amino, *N*-(2-aminocarbonyloxy-1-phenylethyl)-amino, *N*-[1-(fluorophenyl)ethyl]-amino, *N*-[1-(fluorophenyl)-2-hydroxyethyl]-amino, *N*-[1-(fluorophenyl)-2-methoxyethyl]-amino, *N*-[1-(acetylamino-phenyl)ethyl]-amino, *N*-[2-(acetylamino-phenyl)ethyl]-amino, *N*-(2-hydroxy-1-phenylprop-1-yl)-amino, *N*-(1-phenylprop-2-yl)-amino, *N*-(2-phenylprop-2-yl)-amino, *N*-(1-hydroxy-1-phenylprop-2-yl)-amino, *N*-(1-hydroxy-2-phenylprop-2-yl)-amino, *N*-(1-hydroxy-3-phenylprop-2-yl)-amino, *N*-(furylmethyl)-amino, *N*-(pyridylmethyl)-amino, dimethylamino, *N*-isobutyl-*N*-methylamino, *N*-(2,2-dimethylpropyl)-*N*-methylamino, *N*-allyl-*N*-methylamino, *N*-(3,3-dimethylprop-2-en-1-yl)-*N*-methylamino, *N*-(1-cyclohexylethyl)-*N*-methylamino, *N*-benzyl-*N*-methylamino, *N*-methyl-*N*-(methylbenzyl)-amino, *N*-(fluorobenzyl)-*N*-methylamino, *N*-(acetylamino-benzyl)-*N*-methylamino, *N*-methyl-*N*-(1-phenylethyl)-amino, *N*-methyl-*N*-(2-phenylethyl)-amino, *N*-(2-hydroxy-1-phenylethyl)-*N*-methylamino, *N*-(2-methoxy-1-phenylethyl)-*N*-methylamino, *N*-[2-(acetylamino-phenyl)ethyl]-*N*-methylamino, *N*-(furylmethyl)-*N*-methylamino, *N*-methyl-*N*-(thienylmethyl)-amino, *N*-benzyl-*N*-(2-hydroxyethyl)-amino, *N,N*-bis(furylmethyl)-amino, 3,3-dimethylpiperidinyl, 2-phenylpiperidinyl, 3-hydroxy-2-phenylpiperidinyl and 1,2,3,4-tetrahydroisoquinolin-2-yl.

Specific values of R¹ include *N*-benzyl-*N*-methylamino and *N*-methyl-*N*-(1-phenylethyl)-amino.

Particular values of the group R include hydroxy, benzyloxy, benzyloxymethyl, methoxy-benzyloxy, pyridylmethoxy, benzylthio-methyl, fluorobenzylthio-methyl, phenylsulphinylmethyl, benzylsulphinylmethyl, fluorobenzyl-sulphinyl, fluorobenzyl-sulphinylmethyl, fluorobenzyl-sulphonylmethyl, indanylamino, indanylaminomethyl, hydroxyindanyl-amino, benzylamino, benzylaminomethyl, 1-(*N*-benzylamino)-2-hydroxyethyl, *N*-(methylbenzyl)-aminomethyl, *N*-(acetylamino-benzyl)-

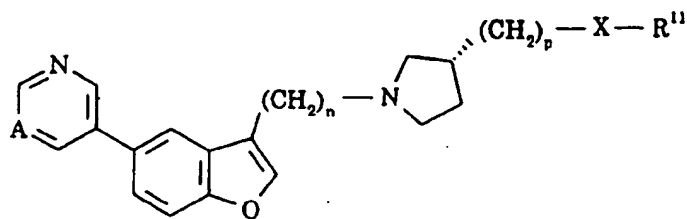
amino, *N*-(acetyl-amino-benzyl)-aminomethyl, *N*-(1-phenylethyl)-amino, *N*-(1-phenylethyl)-aminomethyl, *N*-(2-phenylethyl)-aminomethyl, *N*-(2-hydroxy-1-phenylethyl)-amino, *N*-(2-hydroxy-1-phenylethyl)-aminomethyl, *N*-(2-methoxy-1-phenylethyl)-amino, *N*-(2-aminocarbonyloxy-1-phenylethyl)-amino, *N*-[1-(fluorophenyl)ethyl]-amino, *N*-[1-(fluorophenyl)-2-hydroxyethyl]-amino, *N*-[1-(fluorophenyl)-2-methoxyethyl]-amino, *N*-[1-(acetyl-amino-phenyl)ethyl]-amino, *N*-[1-(acetyl-amino-phenyl)ethyl]-aminomethyl, *N*-[2-(acetyl-amino-phenyl)ethyl]-amino, *N*-(2-hydroxy-1-phenylprop-1-yl)-amino, *N*-(1-phenylprop-2-yl)-amino, *N*-(2-phenylprop-2-yl)-aminomethyl, *N*-(1-hydroxy-1-phenylprop-2-yl)-amino, *N*-(1-hydroxy-2-phenylprop-2-yl)-amino, *N*-(1-hydroxy-3-phenylprop-2-yl)-amino, *N*-(furylmethyl)-amino, *N*-(furylmethyl)-aminomethyl, *N*-(pyridylmethyl)-aminomethyl, *N*-isobutyl-*N*-methyl-aminomethyl, *N*-(2,2-dimethylpropyl)-*N*-methyl-aminomethyl, *N*-allyl-*N*-methyl-amino, *N*-(3,3-dimethylprop-2-en-1-yl)-*N*-methyl-amino, *N*-(1-cyclohexylethyl)-*N*-methyl-aminomethyl, *N*-benzyl-*N*-methyl-amino, *N*-benzyl-*N*-methyl-aminomethyl, *N*-methyl-*N*-(methylbenzyl)-aminomethyl, *N*-(fluorobenzyl)-*N*-methyl-amino, *N*-(acetyl-amino-benzyl)-*N*-methyl-aminomethyl, *N*-methyl-*N*-(1-phenylethyl)-aminomethyl, *N*-methyl-*N*-(2-phenylethyl)-aminomethyl, *N*-(2-hydroxy-1-phenylethyl)-*N*-methyl-amino, *N*-(2-hydroxy-1-phenylethyl)-*N*-methyl-aminomethyl, *N*-(2-methoxy-1-phenylethyl)-*N*-methyl-amino, *N*-[2-(acetyl-amino-phenyl)ethyl]-*N*-methyl-amino, *N*-(furylmethyl)-*N*-methyl-amino, *N*-methyl-*N*-(thienylmethyl)-amino, *N*-benzyl-*N*-(2-hydroxyethyl)-aminomethyl, *N,N*-bis(furylmethyl)-amino, 3,3-dimethylpiperidinylmethyl, 2-phenylpiperidinyl, 2-phenylpiperidinylmethyl, 3-hydroxy-2-phenylpiperidinylmethyl and 1,2,3,4-tetrahydroisoquinolin-2-yl.

Specific values of R include *N*-benzyl-*N*-methyl-amino and *N*-methyl-*N*-(1-phenylethyl)-aminomethyl.

Suitably, R² and R³ independently represent hydrogen or methyl, especially hydrogen.

- 15 -

A particular sub-class of compounds according to the invention is represented by the compounds of formula IIA, and salts and prodrugs thereof:



(IIA)

5 wherein

n is 2, 3 or 4;

p is zero, 1 or 2;

A represents nitrogen or C-R⁵;

10 R⁵ represents hydrogen, C₂₋₄ alkoxy carbonyl, C₁₋₃ alkoxy(C₁₋₃)alkyl or C₁₋₃ alkylsulphonylamino(C₁₋₃)alkyl;

X represents oxygen, sulphur, -SO-, -SO₂- or N-R¹²; and

15 R¹¹ and R¹² independently represent hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, indanyl, aryl, aryl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted.

20 Examples of suitable optional substituents on the groups R¹¹ and R¹² include C₁₋₆ alkyl, halogen, cyano, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, aminocarbonyloxy, C₂₋₆ alkyl carbonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, C₂₋₆ alkyl carbonylamino, C₁₋₆ alkylsulphonylamino and C₁₋₆ alkylaminosulphonylmethyl.

Particular values of R⁵ include hydrogen, methoxycarbonyl, methoxymethyl and methylsulphonylaminomethyl, especially hydrogen.

Suitably, X represents N-R¹².

25 Particular values of R¹¹ and R¹² include hydrogen, methyl, hydroxyethyl, isobutyl, 2,2-dimethylpropyl, allyl, dimethylallyl, 1-cyclohexylethyl, 2-cyclohexylethyl, indanyl, hydroxy-indanyl, phenyl,

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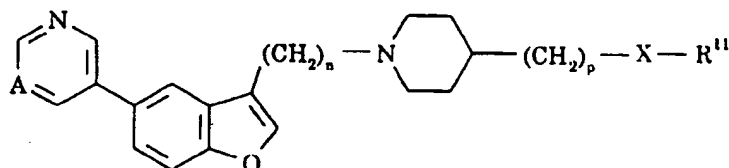
benzyl, methyl-benzyl, fluorobenzyl, methoxy-benzyl, acetamino-benzyl,
 1-phenylethyl, 2-phenylethyl, 2-hydroxy-1-phenylethyl, 2-methoxy-1-
 phenylethyl, 2-aminocarbonyloxy-1-phenylethyl, 1-(fluorophenyl)ethyl, 1-
 (fluorophenyl)-2-hydroxyethyl, 1-(fluorophenyl)-2-methoxyethyl, 1-
 5 (acetamino-phenyl)ethyl, 2-(acetamino-phenyl)ethyl, 2-hydroxy-1-
 phenylprop-1-yl, 1-phenylprop-2-yl, 2-phenylprop-2-yl, 1-hydroxy-1-
 phenylprop-2-yl, 1-hydroxy-2-phenylprop-2-yl, 1-hydroxy-3-phenylprop-2-
 yl, furylmethyl, thienylmethyl and pyridylmethyl.

Specific values of R^{11} and R^{12} include methyl, benzyl and 1-
 10 phenylethyl.

In relation to formula IIA, the variable n is preferably 2.

In relation to formula IIA, the variable p is preferably 1.

Another sub-class of compounds according to the invention is
 represented by the compounds of formula IIB, and salts and prodrugs
 15 thereof:



(IIB)

wherein n , p , A , X and R^{11} are as defined with reference to formula IIA
 above.

In relation to formula IIB, the variable n is preferably 3.

20 In relation to formula IIB, the variable p is suitably zero or 1.

Specific compounds within the scope of the present invention
 include:

N-methyl-*N*-[(1*S*)-1-phenylethyl]-*N*-[(3*R*)-1-(2-(5-(pyridin-3-yl)benzofuran-
 3-yl)ethyl)pyrrolidin-3-ylmethyl]amine;
 25 4-(*N*-benzyl-*N*-methyl)amino-1-[3-(5-(pyridin-3-yl)benzofuran-3-
 yl)propyl]piperidine;

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and salts and prodrugs thereof.

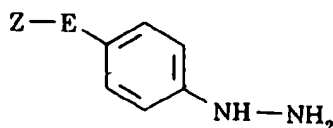
The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A

variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present
5 invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for
10 aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of migraine, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and
15 especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

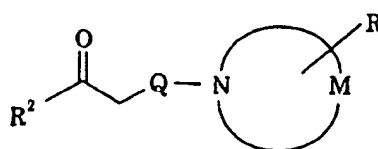
The compounds according to the invention wherein T represents CH, U represents C-R² and V represents N-R³, corresponding to the indole derivatives of formula IF as defined above wherein V¹ represents N-R³,
20 may be prepared by a process which comprises reacting a compound of formula III:



(III)

wherein Z and E are as defined above; with a compound of formula IV, or a carbonyl-protected form thereof:

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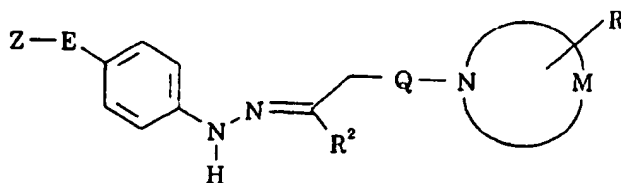
(IV)

wherein R^2 , Q, M and R are as defined above; followed, where required, by N-alkylation by standard methods to introduce the moiety R^3 .

5 The reaction between compounds III and IV, which is an example of the well-known Fischer indole synthesis, is suitably carried out by heating the reagents together under mildly acidic conditions, e.g. 4% sulphuric acid at reflux.

10 Suitable carbonyl-protected forms of the compounds of formula IV include the dimethyl acetal or ketal derivatives. Where the alkylene chain Q is substituted by a hydroxy group, this group may condense with the carbonyl moiety in compound IV whereby the carbonyl moiety is protected in the form of a cyclic hemiacetal.

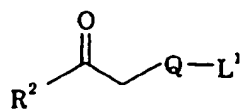
15 The Fischer reaction between compounds III and IV may be carried out in a single step, or may proceed via an initial non-cyclising step at a lower temperature to give an intermediate of formula V:



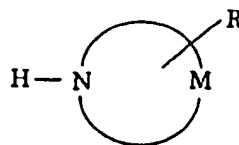
(V)

wherein Z, E, Q, R^2 , M and R are as defined above; followed by cyclisation using a suitable reagent, e.g. a polyphosphate ester.

20 The intermediates of formula IV, or carbonyl-protected forms thereof, may be prepared by reacting a compound of formula VI, or a carbonyl-protected form thereof, with a compound of formula VII:



(VI)



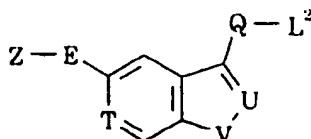
(VII)

wherein Q, R², M and R are as defined above, and L¹ represents a suitable leaving group.

The leaving group L¹ is suitably a halogen atom, e.g. chlorine or
5 bromine.

Where L¹ represents a halogen atom, the reaction between
compounds VI and VII is conveniently effected by stirring the reactants
under basic conditions in a suitable solvent, for example sodium carbonate
or potassium carbonate in 1,2-dimethoxyethane or *N,N*-dimethyl-
10 formamide, or triethylamine in tetrahydrofuran or acetonitrile, optionally
in the presence of catalytic sodium iodide.

In an alternative procedure, the compounds according to the
invention may be prepared by a process which comprises reacting a
compound of formula VII as defined above with a compound of formula
15 VIII:



(VIII)

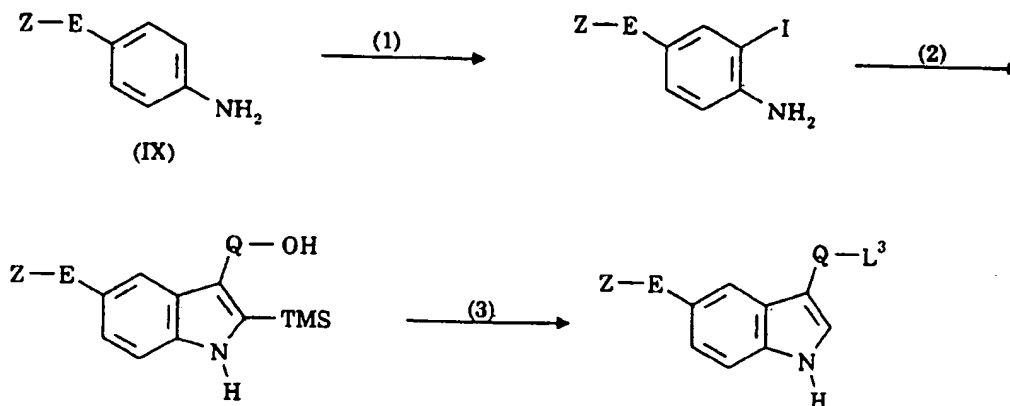
wherein Z, E, Q, T, U and V are as defined above, and L² represents a
suitable leaving group.

The leaving group L² is suitably an alkylsulphonyloxy or
20 arylsulphonyloxy group, e.g. methanesulphonyloxy (mesyloxy) or *p*-
toluenesulphonyloxy (tosyloxy).

Where L² represents an alkylsulphonyloxy or arylsulphonyloxy
group, the reaction between compounds VII and VIII is conveniently
carried out in a suitable solvent such as isopropanol or 1,2-dimethoxy-

ethane, typically in the presence of a base such as sodium carbonate or potassium carbonate, optionally in the presence of sodium iodide.

In one representative approach, the compounds of formula VIII wherein T and U both represent CH, V represents NH and L² represents a mesyloxy or tosyloxy group may be prepared by the sequence of steps illustrated in the following reaction scheme (cf. Larock and Yum, *J. Am. Chem. Soc.*, 1991, 113, 6689):



wherein Z, E and Q are as defined above, L³ represents mesyloxy or tosyloxy, and TMS is an abbreviation for trimethylsilyl.

In Step 1 of the reaction scheme, the aniline derivative IX is treated with iodine monochloride, advantageously in methanol in the presence of a base such as calcium carbonate, in order to introduce an iodine atom *ortho* to the amine moiety. Step 2 involves a palladium-mediated coupling reaction with the protected acetylene derivative TMS-C≡C-Q-OH, typically using palladium acetate and triphenylphosphine in the presence of lithium chloride and sodium carbonate, suitably in *N,N*-dimethyl-formamide at an elevated temperature. This is followed in Step 3 by removal of the TMS moiety, ideally in refluxing methanolic hydrochloric acid; followed in turn by mesylation or tosylation, suitably by using mesyl chloride or tosyl chloride respectively in pyridine.

In another representative approach, the compounds of formula VIII wherein T and U both represent CH, V represents NH, Q represents a propylene chain and L² represents a mesyloxy or tosyloxy group may be

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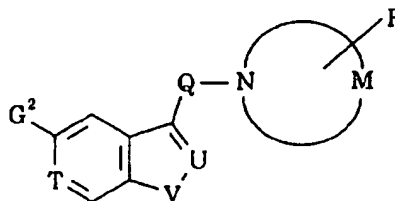
prepared by reacting 3,4-dihydro-2*H*-pyran with a compound of formula III as defined above or a salt thereof, under a variant of the Fischer reaction conditions as described above for the reaction between compounds III and IV; followed by mesylation or tosylation of the 3-hydroxypropyl-indole derivative thereby obtained, typically by treatment with mesyl chloride or tosyl chloride under standard conditions.

The Fischer reaction with 3,4-dihydro-2*H*-pyran is suitably brought about by heating the hydrazine derivative III or an acid addition salt thereof, typically the hydrochloride salt, in an inert solvent such as dioxan, advantageously in the presence of a mineral acid such as hydrochloric acid or a Lewis acid such as zinc chloride, at the reflux temperature of the solvent.

In another procedure, the compounds according to the invention wherein E represents a chemical bond may be prepared by reacting a compound of formula X with a compound of formula XI:



(X)



(XI)

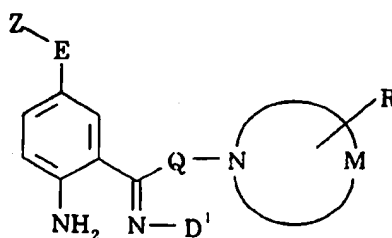
wherein Z, Q, T, U, V, M and R are as defined above; one of G^1 and G^2 represents a suitable leaving group, and the other represents a boronic acid moiety $-B(OH)_2$ or a C_{1-4} alkyl ester or anhydride thereof; in the presence of a transition metal catalyst.

The leaving group G^1 or G^2 is suitably a halogen atom, e.g. bromine.

The transition metal catalyst of use in the reaction between compounds X and XI is suitably tetrakis(triphenylphosphine)palladium (0). The reaction is conveniently carried out in an inert solvent such as

aqueous 1,2-dimethoxyethane, advantageously in the presence of a base such as sodium acetate or sodium carbonate, typically at an elevated temperature.

In a further procedure, the compounds according to the invention wherein T represents CH, U represents nitrogen and V represents N-R³,
 5 corresponding to the indazole derivatives of formula ID as defined above, may be prepared by a process which comprises cyclising a compound of formula XII:



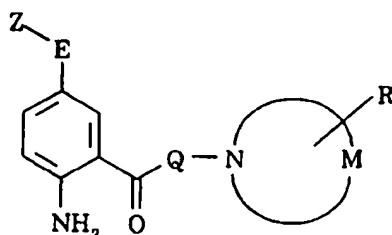
(XII)

10 wherein Z, E, Q, M and R are as defined above, and D¹ represents a readily displaceable group; followed, where required, by N-alkylation by standard methods to introduce the moiety R³.

The cyclisation of compound XII is conveniently achieved in a suitable organic solvent at an elevated temperature, for example in a
 15 mixture of *m*-xylene and 2,6-lutidine at a temperature in the region of 140°C.

The readily displaceable group D¹ in the compounds of formula XII suitably represents a C₁₋₄ alkanoyloxy group, preferably acetoxy. Where D¹ represents acetoxy, the desired compound of formula XII may be
 20 conveniently prepared by treating a carbonyl compound of formula XIII:

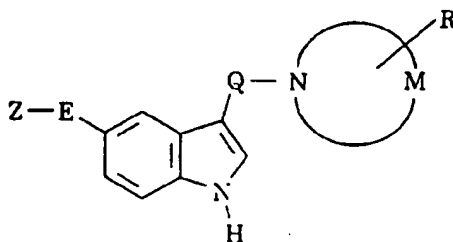
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(XIII)

wherein Z, E, Q, M and R are as defined above; or a protected derivative thereof, preferably the N-formyl protected derivative; with hydroxylamine hydrochloride, advantageously in pyridine at the reflux temperature of the solvent; followed by acetylation with acetic anhydride, advantageously in
 5 the presence of a catalytic quantity of 4-dimethylaminopyridine, in dichloromethane at room temperature.

The N-formyl protected derivatives of the intermediates of formula XIII may conveniently be prepared by ozonolysis of the corresponding
 10 indole derivative of formula XIV:



(XIV)

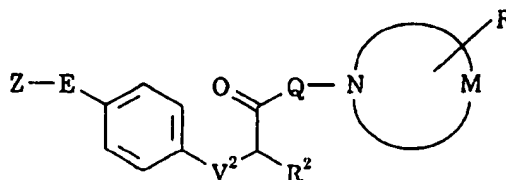
wherein Z, E, Q, M and R are as defined above; followed by a reductive work-up, advantageously using dimethylsulphide.

The indole derivatives of formula XIV may be prepared by methods
 15 analogous to those described in the accompanying Examples, or by procedures well known from the art.

In a still further procedure, the compounds according to the invention wherein T represents CH, U represents C-R² and V represents oxygen or sulphur, corresponding to the benzofuran or benzthiophene
 20 derivatives of formula IC wherein V is oxygen or sulphur respectively, may

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be prepared by a process which comprises cyclising a compound of formula XV:

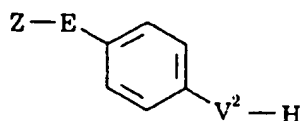


(XV)

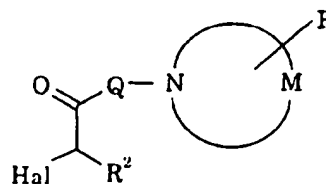
wherein Z, E, Q, R², M and R are as defined above, and V² represents
5 oxygen or sulphur.

The cyclisation of compound XV is conveniently effected by using polyphosphoric acid or a polyphosphate ester, advantageously at an elevated temperature.

The compounds of formula XV may be prepared by reacting a
10 compound of formula XVI with a compound of formula XVII:



(XVI)



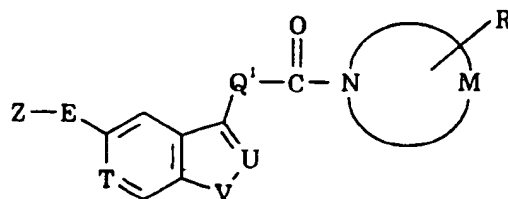
(XVII)

wherein Z, E, Q, R², V², M and R are as defined above, and Hal represents a halogen atom.

The reaction is conveniently effected in the presence of a base such
15 as sodium hydroxide.

In a yet further procedure, the compounds according to the invention may be prepared by a process which comprises reducing a compound of formula XVIII:

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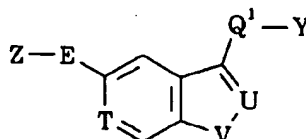


(XVIII)

wherein Z, E, T, U, V, M and R are as defined above, and $-Q^1-CH_2-$ corresponds to the moiety Q as defined above.

The reaction is suitably carried out by treating the compound of formula XVIII with a reducing agent such as lithium aluminium hydride in an appropriate solvent, e.g. diethyl ether, tetrahydrofuran or mixtures thereof.

The compounds of formula XVIII above may suitably be prepared by reacting a compound of formula VII as defined above with the appropriate compound of formula XIX:



(XIX)

wherein Z, E, T, U, V and Q^1 are as defined above, and Y represents a reactive carboxylate moiety.

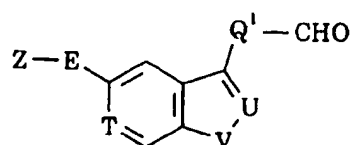
Suitable values for the reactive carboxylate moiety Y include esters, for example C_{1-4} alkyl esters; acid anhydrides, for example mixed anhydrides with C_{1-4} alkanolic acids; acid halides, for example acid chlorides; and acylimidazoles.

By way of example, the intermediates of formula XIX above wherein Y is an acid chloride moiety may be prepared by treating the corresponding carboxylic acid derivative with thionyl chloride in toluene. Similarly, the intermediates of formula XIX wherein Y is an acylimidazole moiety may be prepared by treating the corresponding carboxylic acid

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derivative with 1,1'-carbonyldiimidazole. Alternatively, the reactive carboxylate moiety Y may be obtained by treating the corresponding compound wherein Y is carboxy with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole hydrate,
 5 optionally in the presence of triethylamine; the resulting activated carboxylate intermediate may then suitably be reacted *in situ* with the required compound of formula VII.

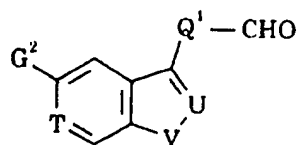
In one additional procedure, the compounds according to the invention may be prepared by a process which comprises reacting a
 10 compound of formula VII as defined above with a compound of formula XX:



(XX)

wherein Z, E, T, U, V and Q¹ are as defined above; in the presence of a reducing agent.

Similarly, the compounds of formula XI above may be prepared by
 15 reacting a compound of formula VII as defined above with a compound of formula XXI:

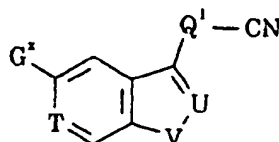


(XXI)

wherein T, U, V, G² and Q¹ are as defined above; in the presence of a reducing agent.

20 A suitable reducing agent for use in conjunction with the above reaction between compound VII and compound XX or XXI is sodium triacetoxyborohydride, in which case the reaction is conveniently effected in the presence of acetic acid and a solvent such as dichloromethane.

The compounds of formula XX and XXI may be prepared by reduction of the appropriate compound of formula XXII:

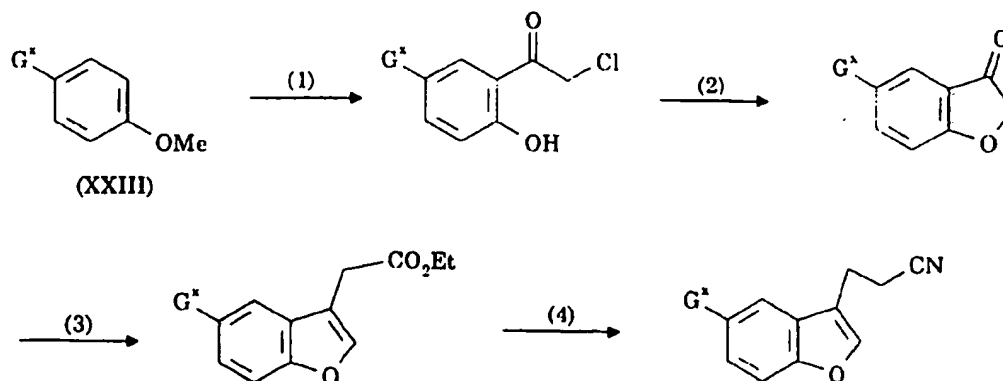


(XXII)

wherein T, U, V and Q¹ are as defined above; and G^x corresponds to the moiety Z-E- as defined above, or G^x corresponds to the group of formula G² as defined above.

A suitable reducing agent for effecting the transformation of the cyano moiety in compound XXII to the carboxaldehyde (CHO) moiety in compounds XX and XXI is diisobutylaluminium hydride (DIBAL-H), and the reaction is conveniently carried out in a solvent such as dichloromethane.

A representative approach to the nitrile intermediates of formula XXII in which T and U both represent CH, V is oxygen and Q¹ is an ethylene linkage can be illustrated as follows:



in which G^x is as defined above.

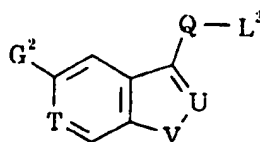
In Step 1, the anisole derivative XXIII is treated with chloroacetyl chloride in the presence of aluminium chloride, whereby the methoxy substituent is demethylated, with concomitant introduction of the chloroacetyl moiety *ortho* to the resulting phenolic OH. This compound is then cyclised in Step 2, by treatment with methanolic sodium acetate at

an elevated temperature. Step 3 comprises treatment of the resulting furanone derivative with triethyl phosphonoacetate in the presence of a strong base such as potassium hexamethyldisilazide, followed in Step 4 by

- 5 The hydroxyethyl benzofuran derivative thereby obtained is mesylated, and the mesyl group thereof subsequently displaced by cyanide ion, to afford the desired cyanoethyl benzofuran analogue.

The intermediates of formula XI above may suitably be prepared by reacting a compound of formula VII as defined above with a compound of

- 10 formula XXIV:



(XXIV)

wherein Q, T, U, V, L² and G² are as defined above; under conditions analogous to those described above for the reaction between compounds VII and VIII.

- 15 Typical intermediates of formula XXIV, wherein T and U are both CH, V is oxygen, Q is an ethylene linkage and L² is mesyl or tosyl, can be prepared from compound XXIII, in which G^x corresponds to the group G², by following Steps 1 to 3 of the reaction scheme illustrated immediately above to obtain the ethyl ester intermediate, which can then be reduced
- 20 with DIBAL-H and mesylated or tosylated under standard conditions.

Where they are not commercially available, the starting materials of formula III, VI, VII, IX, X, XVI, XVII, XIX and XXIII may be prepared by the methods described in the accompanying Examples, or by analogous procedures which will be apparent to those skilled in the art.

- 25 It will be understood that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula I by techniques known from the art. For example, a compound of formula I

- 30 -

wherein R^x is benzyl initially obtained may be converted into a compound of formula I wherein R^x is hydrogen typically by conventional catalytic hydrogenation, or by transfer hydrogenation using a hydrogenation catalyst such as palladium on charcoal in the presence of a hydrogen donor
5 such as ammonium formate. Moreover, a compound of formula I wherein R^1 is hydroxy initially obtained may be converted into the corresponding carbonyl compound (aldehyde or ketone) by treatment with a conventional oxidising agent such as sulphur trioxide-pyridine complex; the resulting carbonyl compound may then be converted in turn into a compound of
10 formula I wherein R^1 represents $-NHR^y$, suitably by a standard reductive amination procedure which comprises treating the carbonyl compound with the appropriate amine of formula R^y-NH_2 in the presence of a suitable reducing agent, typically sodium cyanoborohydride. Furthermore, a compound of formula I wherein R^1 represents $-NHR^y$ initially obtained
15 may be converted into a further compound of formula I wherein R^1 represents $-NR^xR^y$, in which R^x corresponds to the group $-CH_2R^z$, suitably by a reductive amination procedure which comprises treating the compound of formula I wherein R^1 represents $-NHR^y$ with the appropriate aldehyde of formula R^z-CHO in the presence of a reducing agent such as
20 sodium cyanoborohydride. In addition, a compound of formula I wherein R^3 is hydrogen initially obtained may be converted into a compound of formula I wherein R^3 represents C_{1-6} alkyl by standard alkylation techniques, for example by treatment with an alkyl iodide, e.g. methyl iodide, typically under basic conditions, e.g. sodium hydride in
25 dimethylformamide.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The novel compounds may be
30 prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds

may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-*p*-toluoyl-d-tartaric acid and/or (+)-di-*p*-toluoyl-l-tartaric acid, followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The compounds in accordance with the present invention potently and selectively bind to the 5-HT_{1D α} receptor subtype, inhibit forskolin-stimulated adenylyl cyclase activity, and stimulate [³⁵S]-GTP γ S binding to membranes from clonal cell lines expressing human cloned receptors.

5-HT_{1D α} /5-HT_{1D β} Radioligand Binding

Chinese hamster ovary (CHO) clonal cell lines expressing the human 5-HT_{1D α} and 5-HT_{1D β} receptors were harvested in PBS and homogenised in ice cold 50 mM Tris-HCl (pH 7.7 at room temperature) with a Kinematica polytron and centrifuged at 48,000g at 4°C for 11 min. The pellet was then resuspended in 50 mM Tris-HCl followed by a 10 min incubation at 37°C. Finally the tissue was recentrifuged at 48,000g, 4°C

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for 11 min and the pellet resuspended, in assay buffer (composition in mM: Tris-HCl 50, pargyline 0.01, CaCl_2 4; ascorbate 0.1%; pH 7.7 at room temperature) to give the required volume immediately prior to use (0.2 mg protein/ml). Incubations were carried out for 30 min at 37°C in the presence of 0.02-150 nM [^3H]-5-HT for saturation studies or 2-5 nM [^3H]-5-HT for displacement studies. The final assay volume was 1 ml. 5-HT (10 μM) was used to define non-specific binding. The reaction was initiated by the addition of membrane and was terminated by rapid filtration through Whatman GF/B filters (presoaked in 0.3% PEI/ 0.5% Triton X) followed by 2 x 4 ml washings with 50 mM Tris-HCl. The radioactive filters were then counted on a LKB beta or a Wallac beta plate counter. Binding parameters were determined by non-linear, least squares regression analysis using an iterative curve fitting routine, from which IC_{50} (the molar concentration of compound necessary to inhibit binding by 50%) values could be calculated for each test compound. The IC_{50} values for binding to the 5-HT $_{1D\alpha}$ receptor subtype obtained for the compounds of the accompanying Examples were below 50 nM in each case. Furthermore, the compounds of the accompanying Examples were all found to possess a selective affinity for the 5-HT $_{1D\alpha}$ receptor subtype of at least 10-fold relative to the 5-HT $_{1D\beta}$ subtype.

5-HT $_{1D\alpha}$ /5-HT $_{1D\beta}$ Adenylyl Cyclase Assay

Studies were performed essentially as described in *J. Pharmacol. Exp. Ther.*, 1986, 238, 248. CHO clonal cell lines expressing the human cloned 5-HT $_{1D\alpha}$ and 5-HT $_{1D\beta}$ receptors were harvested in PBS and homogenised, using a motor driven teflon/glass homogeniser, in ice cold Tris HCl-EGTA buffer (composition in mM: Tris HCl 10, EGTA 1, pH 8.0 at room temperature) and incubated on ice for 30-60 min. The tissue was then centrifuged at 20,000g for 20 min at 4°C, the supernatant discarded and the pellet resuspended in Tris HCl-EDTA buffer (composition in mM:

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Tris HCl 50, EDTA 5, pH 7.6 at room temperature) just prior to assay. The adenylyl cyclase activity was determined by measuring the conversion of α -[^{33}P]-ATP to [^{33}P]-cyclic AMP. A 10 μl aliquot of the membrane suspension was incubated, for 10-15 min, in a final volume of 50 μl , at 5 30°C, with or without forskolin (10 μM), in the presence or absence of test compound. The incubation buffer consisted of 50 mM Tris HCl (pH 7.6 at room temperature), 100 mM NaCl, 30 μM GTP, 50 μM cyclic AMP, 1 mM dithiothreitol, 1 mM ATP, 5 mM MgCl_2 , 1 mM EGTA, 1 mM 3-isobutyl-1-methylxanthine, 3.5 mM creatinine phosphate, 0.2 mg/ml creatine 10 phosphokinase, 0.5-1 μCi α -[^{33}P]-ATP and 1 nCi [^3H]-cyclic AMP. The incubation was initiated by the addition of membrane, following a 5 min preincubation at 30°C, and was terminated by the addition of 100 μl SDS (composition in mM: sodium lauryl sulphate 2%, ATP 45, cyclic AMP 1.3, pH 7.5 at room temperature). The ATP and cyclic AMP were separated on 15 a double column chromatography system (*Anal. Biochem.*, 1974, 58, 541). Functional parameters were determined using a least squares curve fitting programme ALLFIT (*Am. J. Physiol.*, 1978, 235, E97) from which E_{max} (maximal effect) and EC_{50} (the molar concentration of compound necessary to inhibit the maximal effect by 50%) values were obtained for 20 each test compound. Of those compounds which were tested in this assay, the EC_{50} values for the 5-HT $_{1D\alpha}$ receptor obtained for the compounds of the accompanying Examples were below 500 nM in each case. Moreover, the compounds of the accompanying Examples which were tested were all found to possess at least a 10-fold selectivity for the 5-HT $_{1D\alpha}$ receptor 25 subtype relative to the 5-HT $_{1D\beta}$ subtype.

5-HT $_{1D\alpha}$ /5-HT $_{1D\beta}$ GTP γ S Binding

Studies were performed essentially as described in *Br. J. Pharmacol.*, 1993, 109, 1120. CHO clonal cell lines expressing the human 30 cloned 5-HT $_{1D\alpha}$ and 5-HT $_{1D\beta}$ receptors were harvested in PBS and

homogenised using a Kinematica polytron in ice cold 20 mM HEPES containing 10 mM EDTA, pH 7.4 at room temperature. The membranes were then centrifuged at 40,000g, 4°C for 15 min. The pellet was then resuspended in ice cold 20 mM HEPES containing 0.1 mM EDTA, pH 7.4 at room temperature and recentrifuged at 40,000g, 4°C for 15-25 minutes. The membranes were then resuspended in assay buffer (composition in mM: HEPES 20, NaCl 100, MgCl₂ 10, pargyline 0.01; ascorbate 0.1%; pH 7.4 at room temperature) at a concentration of 40 µg protein/ml for the 5-HT_{1D α} receptor transfected cells and 40-50 µg protein/ml for the 5-HT_{1D β} receptor transfected cells. The membrane suspension was then incubated, in a volume of 1 ml, with GDP (100 µM for 5-HT_{1D α} receptor transfected cells, 30 µM for the 5-HT_{1D β} receptor transfected cells) and test compound at 30°C for 20 min and then transferred to ice for a further 15 min. [³⁵S]-GTP γ S was then added at a final concentration of 100 pM and the samples incubated for 30 min at 30°C. The reaction was initiated by the addition of membrane and was terminated by rapid filtration through Whatman GF/B filters and washed with 5 ml water. The radioactive filters were then counted on a LKB beta counter. Functional parameters were determined by a non-linear, least squares regression analysis using an iterative curve fitting routine, from which E_{max} (maximal effect) and EC₅₀ (the molar concentration of compound necessary to inhibit the maximal effect by 50%) values were obtained for each test compound. Of those compounds which were tested in this assay, the EC₅₀ values for the 5-HT_{1D α} receptor obtained for the compounds of the accompanying Examples were below 500 nM in each case. Moreover, the compounds of the accompanying Examples which were tested were all found to possess at least a 10-fold selectivity for the 5-HT_{1D α} receptor subtype relative to the 5-HT_{1D β} subtype.

EXAMPLE 1

N-Methyl-N-[(1S)-1-phenylethyl]-N-[(3R)-1-(2-(5-(pyridin-3-yl)benzofuran-3-yl)ethyl)pyrrolidin-3-ylmethyl]amine 3 hydrogen oxalate

5

Step 1: 1-(5-Bromo-2-hydroxyphenyl)-2-chloroethanone

To a solution of 4-bromoanisole (17.4 ml, 138 mmol) in dichloromethane (150 ml) was added chloroacetyl chloride (32 ml, 400 mmol) followed by aluminium chloride (60 g, 450 mmol) keeping the temperature below 30°C. The yellow solution was heated to reflux for 8 hours, cooled down to ambient temperature, then ice water was added very carefully. The organic layer was separated and the aqueous extracted once with dichloromethane. The combined organics were dried (sodium sulphate) then evaporated to give an oil which was purified by crystallisation from hexane. The title compound was obtained as a yellow solid (18 g, 52%). mp 80-82°C. ¹H NMR (250MHz, CDCl₃) δ 4.69 (2H, s), 6.95 (1H, d, J=9Hz), 7.60 (1H, dd, J=1 and 9Hz), 7.80 (1H, d, J=2Hz), 11.59 (1H, s).

20 Step 2: 5-Bromobenzofuran-3-one

To a solution of the foregoing ethanone (18 g, 72 mmol) in methanol (150 ml) was added sodium acetate (7g, 85 mmol). The solution was heated at 65°C for 1 hour, then the methanol was evaporated. The residue was partitioned between dichloromethane and water. The organic layer was separated and the aqueous solution reextracted once with dichloromethane. The combined organics were dried (sodium sulphate) then evaporated to give a gum which was purified by column chromatography on alumina using dichloromethane to afford a solid (5.6 g, 36%). mp 102-106°C. ¹H NMR (250MHz, CDCl₃) δ 4.67 (2H, s), 7.05 (1H, d, J=9Hz), 7.69 (1H, dd, J=2 and 9Hz), 7.79 (H, d, J=2Hz).

30

Step 3: 5-Bromobenzofuran-3-ylacetic acid ethyl ester

To a solution of triethyl phosphonoacetate (6 ml, 30.2 mmol) in dry tetrahydrofuran (200 ml) at -78°C was added a solution of potassium bis(trimethylsilyl)amide in toluene (58 ml of a 0.5M solution). After stirring for 2 hours at -78°C, 5-bromobenzofuran-3-one (5.5g, 26 mmol) was added dropwise. The resulting solution was stirred 1 hour at -78°C and overnight at room temperature. Saturated aqueous ammonium chloride solution and ethyl acetate were added. The organic layer was separated and evaporated to dryness to give the crude title compound which was purified by column chromatography on silica using dichloromethane, followed by column chromatography on alumina using dichloromethane. 5-Bromobenzofuran-3-ylacetic acid ethyl ester was obtained as a low melting solid (4.2g, 57%). mp 38-40°C. ¹H NMR (250MHz, CDCl₃) δ 1.28 (3H, t, J=7Hz), 3.65 (2H, d, J=1Hz), 4.20 (2H, q, J=7Hz), 7.36 (1H, s), 7.38 (1H, d, J=2Hz), 7.63 (1H, s), 7.71 (1H, d, J=2Hz).

Step 4: 2-(5-Bromobenzofuran-3-yl)ethanol

To a solution of the foregoing ester (2.2 g, 7.8 mmol) in toluene (150 ml) under nitrogen at 5°C was added diisobutylaluminium hydride in toluene (20 ml of a 1M solution). The solution was stirred 1 hour at 5°C and 1 hour at ambient temperature, then methanol was added slowly followed by 10% aqueous potassium carbonate solution. The organic layer was decanted and the aqueous reextracted with ethyl acetate. The combined organics were filtered and evaporated to dryness to give the title compound (1.8 g, 96%) as an oil. ¹H NMR (360MHz, d₆-DMSO) δ 2.78 (2H, dt, J=1 and 7Hz), 3.68 (2H, dt, J=5 and 7Hz), 4.73 (1H, t, J=5Hz), 7.43 (1H, dd, J=2 and 9Hz), 7.53 (1H, d, J=9Hz), 7.84 (1H, s), 7.88 (1H, d, J=2Hz).

Step 5: N-Methyl-N-[(3R)-1-(2-(5-bromobenzofuran-3-yl)ethyl)pyrrolidin-3-ylmethyl]-N-[(1S)-1-phenylethyl]amine

To a solution of 2-(5-bromobenzofuran-3-yl)ethanol (200 mg, 0.95 mmol) in dichloromethane (10 ml) at -5°C under nitrogen was added
5 triethylamine (0.21 ml, 1.5 mmol) followed by methanesulphonyl chloride (0.11 ml, 1.4 mmol). The solution was stirred for 20 minutes at -5°C, then washed twice with water, dried (sodium sulphate) and evaporated to give the mesylate which was redissolved in tetrahydrofuran (20 ml). N-Methyl-N-(1(S)-1-phenylethyl)-N-(pyrrolidin-3(R)-ylmethyl)amine (220 mg, 1
10 mmol) (WO 96/04274) was added followed by potassium carbonate (138 mg, 1 mmol) and the solution was heated to reflux for 24 hours. The solvent was evaporated and the residue partitioned between dichloromethane and water. The organic layer was separated, dried (sodium sulphate), evaporated and the oil purified by column
15 chromatography on silica using a methanol/dichloromethane gradient to give the title compound (110 mg, 24%) as an oil. ¹H NMR (250MHz, CDCl₃) δ 1.35 (3H, d, J=7Hz), 1.40-1.57 (1H, m), 1.88-2.10 (1H, m), 2.19 (3H, s), 2.22-2.64 (5H, m), 2.66-2.94 (6H, m), 3.62 (1H, q, J=7Hz), 7.18-7.42 (7H, m), 7.45 (1H, s), 7.68 (1H, d, J=2Hz). MS, m/z=441 and 443 for
20 (M+H)⁺.

Step 6: N-Methyl-N-[(1S)-1-phenylethyl]-N-[(3R)-1-(2-(5-(pyridin-3-yl)benzofuran-3-yl)ethyl)pyrrolidin-3-ylmethyl]amine 3 hydrogen oxalate

To a solution of the foregoing 5-bromobenzofuran (100 mg, 0.23
25 mmol) in ethylene glycol dimethyl ether (10 ml) was added 3-pyridyl boronic acid (36 mg, 0.3 mmol) (Tarashima M. *et al.*, Japan. Chem. Phar. Bull. 1983, 31(12), 4573), sodium acetate (65 mg, 0.61 mmol) and water (5 ml). The solution was purged with nitrogen for 2 hours. Tetrakis(triphenylphosphine)palladium (0) (200 mg) was added and the
30 mixture stirred for 2 hours at reflux. After cooling down to ambient temperature, 10% aqueous sodium carbonate was added and the mixture

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extracted twice with ethyl acetate. The combined organics were washed with brine, dried (sodium sulphate) and evaporated. The residue was purified by column chromatography on silica using a methanol/dichloromethane gradient. The title compound was obtained as an oil (78 mg, 77%). The hydrogen oxalate had mp 75°C (decomposition). ¹H NMR (360MHz, d₆-DMSO) δ 1.43 (3H, d, J=7Hz), 1.60-1.74 (1H, m), 2.08-2.23 (1H, m), 2.29 (3H, s), 2.56-2.75 (3H, m), 3.00-3.10 (1H, m), 3.13 (2H, t, J=7Hz), 3.27-3.60 (3H, m), 3.46 (2H, t, J=7Hz), 3.97 (1H, q, J=7Hz), 7.27-7.46 (5H, m), 7.51 (1H, dd, J=5 and 8Hz), 7.71 (2H, s), 7.97 (1H, s), 8.09 (1H, s), 8.15 (1H, dd, J=2 and 8Hz), 8.59 (1H, dd, J=2 and 5Hz), 8.98 (1H, d, J=2Hz). MS, m/z=440 for (M+H)⁺. (Found: C, 55.59; H, 6.15; N, 5.74. C₂₉H₃₃N₃O. 3(CO₂H)₂. 2.5H₂O requires C, 55.70; H, 5.88; N, 5.57%).

EXAMPLE 2

15

4-(N-Benzyl-N-methylamino)-1-[3-(5-(pyridin-3-yl)benzofuran-3-yl)propyl]-piperidine 3 hydrogen oxalate

Step 1: 1-tert-Butyloxycarbonyl-4-(N-benzyl-N-methylamino)piperidine

20 To a stirred solution of 1-tert-butyloxycarbonyl-4-piperidone (3.30g, 16.5mmol) and benzylamine (1.64ml, 15.0mmol) in a mixture of methanol (150ml) and glacial acetic acid (3.4ml, 60mmol) was added sodium cyanoborohydride (1.04g, 16.5mmol), and the resulting mixture was stirred at room temperature for 2 hours 15 minutes. A solution of
25 formaldehyde (38% w/v aqueous solution; 1.42ml) in methanol (5ml) was added and stirring was continued for 16 hours. 4N Sodium hydroxide (35ml) was added and the methanol was removed under vacuum. The residue was diluted with water (50ml) and products were extracted with diethyl ether (2x300ml). The combined organic phases were washed with
30 brine (50ml), dried (Na₂SO₄) and concentrated. Flash chromatography of the residue (silica gel, dichloromethane - methanol - ammonia, 97:3:0.2)

followed by repurification of impure fractions on alumina (activity III, dichloromethane) afforded 3.98g (87.4%) of the *title compound* as a colourless thick oil; δ_H (360MHz, $CDCl_3$) 1.46 (9H, s), 1.44-1.56 (2H, m), 1.76-1.85 (2H, m), 2.20 (3H, s), 2.52-2.76 (3H, m), 3.57 (2H, s), 4.10-4.22 (2H, m), 7.20-7.36 (5H, m); m/e (ES) 305 ($M^+ + 1$).

Step 2: 4-(N-Benzyl-N-methylamino)piperidine

A solution of the preceding piperidine (3.95g, 12.97mmol) in a mixture of dichloromethane (40ml) and trifluoroacetic acid (40ml) was allowed to stand at room temperature for 3 hours. Solvents were removed under vacuum and the residue azotroped with toluene-methanol (5:1, 100ml). The remaining residue was dissolved in 4N sodium hydroxide (50ml) and extracted with dichloromethane (2x150ml). The combined organic solutions were washed with brine (50ml), dried (Na_2SO_4) and concentrated to give the *title compound* (2.70g, 100%) which was used in the next step without further purification; δ_H (360MHz, $CDCl_3$) 1.52 (2H, dq, $J=12.2$ and 4.0 Hz), 1.80-1.90 (2H, m), 2.21 (3H, s), 2.50-2.66 (3H, m), 3.12-3.22 (2H, m), 3.58 (2H, s), 7.18-7.36 (5H, m); m/e (ES) 205 ($M^+ + 1$).

Step 3: 4-(N-Benzyl-N-methylamino)-1-[3-(5-bromobenzofuran-3-yl)propyl]piperidine

The title compound was obtained following the procedure described in Example 1 Step 5 using the amine from Example 2 Step 2. 1H NMR (250MHz, $CDCl_3$) δ 1.72-2.00 (6H, m), 2.20 (3H, s), 2.32-2.46 (2H, m), 2.54-2.72 (3H, m), 2.92-3.06 (4H, m), 3.57 (2H, s), 7.20-7.42 (7H, m), 7.69 (1H, s), 7.70 (1H, s). MS, m/z=441 and 443 for ($M+H$) $^+$.

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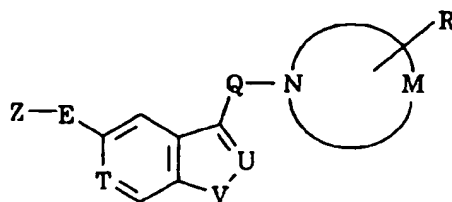
Step 4: 4-(N-Benzyl-N-methylamino)-1-[3-(5-(pyridin-3-yl)benzofuran-3-yl)propyl]piperidine 3 hydrogen oxalate

The title compound was obtained following the procedure described in Example 1 Step 6 using the 5-bromobenzofuran from Example 2 Step 3.

- 5 The hydrogen oxalate salt had mp>192°C. ¹H NMR (360MHz, d₆-DMSO) δ 1.88-2.03 (2H, m), 2.03-2.17 (4H, m), 2.33 (3H, s), 2.71-2.83 (2H, m), 2.83-2.97 (2H, m), 2.97-3.12 (3H, m), 3.43-3.58 (2H, m), 3.92 (2H, s), 7.26-7.46 (5H, m), 7.46-7.56 (1H, m), 7.60-7.70 (2H, m), 7.90 (1H, s), 8.01 (1H, s), 8.09-8.17 (1H, m), 8.57 (1H, dd, J=2Hz and 5Hz), 8.96 (1H, d, J=2Hz). MS, m/z=440 for (M+H)⁺. (Found: C, 59.06; H, 5.77; N, 5.73. C₂₉H₃₃N₃O 3(CO₂H)₂ requires C, 59.23; H, 5.54; N, 5.92%).
- 10

CLAIMS:

1. A compound of formula I, or a salt or prodrug thereof:



(I)

5 wherein

Z represents an optionally substituted six-membered heteroaromatic ring selected from pyridine, pyrazine, pyrimidine and pyridazine;

10 E represents a chemical bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

Q represents a straight or branched alkylene chain containing from 1 to 4 carbon atoms, optionally substituted in any position by one or more substituents selected from fluoro and hydroxy;

T represents nitrogen or CH;

15 U represents nitrogen or C-R²;

V represents oxygen, sulphur or N-R³;

R² and R³ independently represent hydrogen or C₁₋₆ alkyl;

M represents the residue of an azetidine, pyrrolidine or piperidine ring;

20 R represents a group of formula -W-R¹;

W represents a chemical bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms, optionally substituted in any position by a hydroxy group;

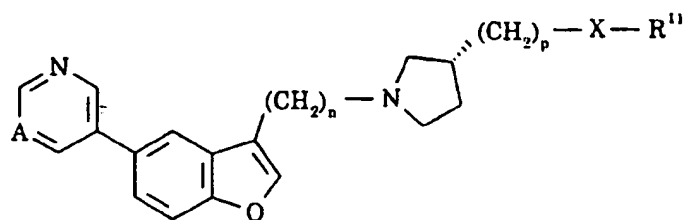
R¹ represents -OR^x, -SR^x, -SOR^x, -SO₂R^x or -NR^xR^y; and

25 R^x and R^y independently represent hydrogen, hydrocarbon or a heterocyclic group; or R^x and R^y together represent a C₂₋₆ alkylene group,

- 42 -

which alkylene group may be optionally substituted by one or more substituents selected from C₁₋₆ alkyl, aryl and hydroxy, or fused with a phenyl ring.

- 5 2. A compound as claimed in claim 1 represented by formula IIA, and salts and prodrugs thereof:



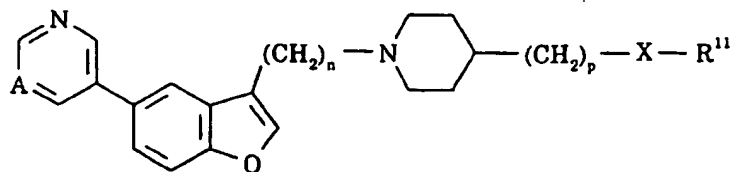
(IIA)

wherein

- n is 2, 3 or 4;
- 10 p is zero, 1 or 2;
- A represents nitrogen or C-R⁵;
- R⁵ represents hydrogen, C₂₋₄ alkoxy carbonyl, C₁₋₃ alkoxy(C₁₋₃)alkyl or C₁₋₃ alkylsulphonylamino(C₁₋₃)alkyl;
- X represents oxygen, sulphur, -SO-, -SO₂- or N-R¹²; and
- 15 R¹¹ and R¹² independently represent hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, indanyl, aryl, aryl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted.

- 20 3. A compound as claimed in claim 1 represented by formula IIB, and salts and prodrugs thereof:

- 43 -



(IIB)

wherein n, p, A, X and R¹¹ are as defined in claim 2.

4. A compound selected from:

- 5 *N*-methyl-*N*-[(1*S*)-1-phenylethyl]-*N*-[(3*R*)-1-(2-(5-(pyridin-3-yl)benzofuran-3-yl)ethyl)pyrrolidin-3-ylmethyl]amine;
 4-(*N*-benzyl-*N*-methyl)amino-1-[3-(5-(pyridin-3-yl)benzofuran-3-yl)propyl]piperidine;
 and salts and prodrugs thereof.

10

5. A pharmaceutical composition comprising a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof or a prodrug thereof in association with a pharmaceutically acceptable carrier.

15

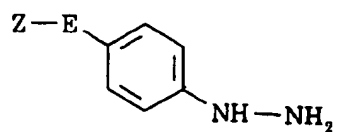
6. A compound as claimed in any one of claims 1 to 4 for use in therapy.

7. The use of a compound as claimed in any one of claims 1 to 4
 20 for the manufacture of a medicament for the treatment and/or prevention of clinical conditions for which an agonist of 5-HT_{1D} receptors selective for the 5-HT_{1Dα} subtype thereof is indicated.

8. A process for the preparation of a compound as claimed in
 25 claim 1, which comprises:

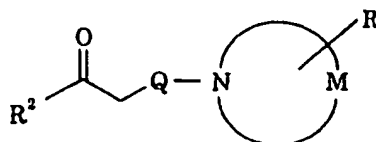
- 44 -

(A) reacting a compound of formula III:



(III)

wherein Z and E are as defined in claim 1; with a compound of formula IV,
or a carbonyl-protected form thereof:



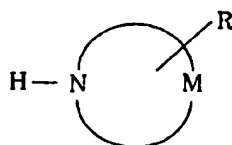
(IV)

5

wherein R², Q, M and R are as defined in claim 1; followed, where
required, by N-alkylation by standard methods to introduce the moiety R³;
or

10

(B) reacting a compound of formula VII:

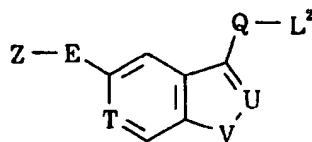


(VII)

wherein M and R are as defined in claim 1; with a compound of formula

15

VIII:



(VIII)

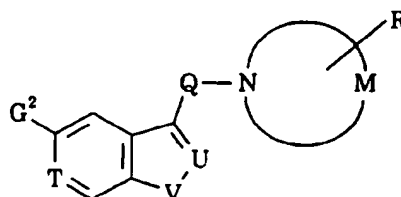
- 45 -

wherein Z, E, Q, T, U and V are as defined in claim 1, and L² represents a suitable leaving group; or

(C) reacting a compound of formula X with a compound of formula
 5 XI:



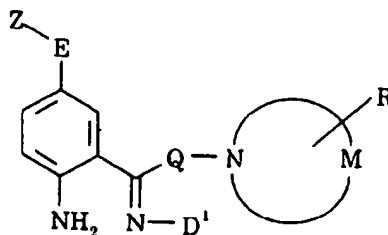
(X)



(XI)

wherein Z, Q, T, U, V, M and R are as defined in claim 1; one of G¹ and G²
 10 represents a suitable leaving group, and the other represents a boronic acid moiety -B(OH)₂ or a C₁₋₄ alkyl ester or anhydride thereof; in the presence of a transition metal catalyst; or

(D) cyclising a compound of formula XII:



(XII)

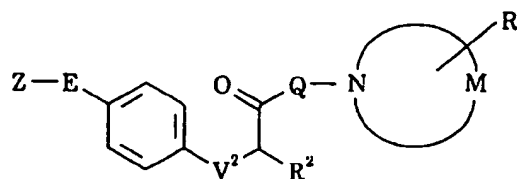
15

wherein Z, E, Q, M and R are as defined in claim 1, and D¹ represents a readily displaceable group; followed, where required, by N-alkylation by standard methods to introduce the moiety R³; or

20

(E) cyclising a compound of formula XV:

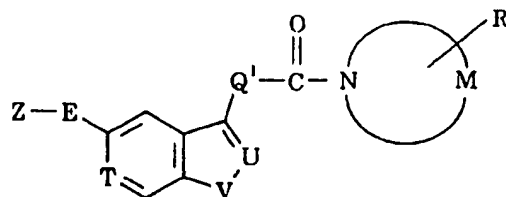
- 46 -



(XV)

wherein Z, E, Q, R², M and R are as defined in claim 1, and V² represents oxygen or sulphur; or

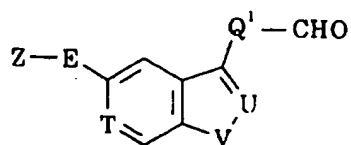
- 5 (F) reducing a compound of formula XVIII:



(XVIII)

wherein Z, E, T, U, V, M and R are as defined in claim 1, and -Q¹-CH₂- corresponds to the moiety Q as defined in claim 1; or

- 10 (G) reacting a compound of formula VII as defined above with a compound of formula XX:



(XX)

wherein Z, E, T, U and V are as defined in claim 1, and Q¹ is as defined above; in the presence of a reducing agent; and

15

(H) if required, converting a compound of formula I initially obtained into a further compound of formula I by conventional methods.

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9. A method for the treatment and/or prevention of clinical conditions for which an agonist of 5-HT_{1D} receptors selective for the 5-HT_{1D α} subtype thereof is indicated, which method comprises
- 5 administering to a patient in need of such treatment an effective amount of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof or a prodrug thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/01330

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D405/14 A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC.

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 08993 A (GLAXO GROUP LTD ;NORTH PETER CHARLES (GB); WADMAN SJOERD NICOLAAS) 28 April 1994 see claim 1 ---	1
Y	WO 96 04274 A (MERCK SHARP & DOHME ;BAKER RAYMOND (GB); BOURRAIN SYLVIE (GB); CAS) 15 February 1996 see claim 1 ---	1-8
Y	WO 95 28400 A (GLAXO GROUP LTD ;NORTH PETER CHARLES (GB); WADMAN SJOERD NICOLAAS) 26 October 1995 see claim 1 --- -/-	1-8

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

A document member of the same patent family

Date of the actual completion of the international search

25 July 1997

Date of mailing of the international search report

02.10.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer

Gettins, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 97/01330

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>WO 95 32196 A (MERCK SHARP & DOHME ;CASTRO PINEIRO JOSE LUIS (GB); CHAMBERS MARK) 30 November 1995 see claim 1</p> <p>-----</p>	1-8

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Information on patent family members

International Application No

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